

## REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the following comments.

Claims 18, 19 and 43, as renumbered, were rejected under 35 USC § 102(b) as being anticipated by Alburger, US 3,506,827. In response, Applicants would remind the Examiner that anticipation requires that each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference, and, further, if the Examiner relies on a theory of inherency as to any particular element, then the extrinsic evidence must make clear that such element is *necessarily* present in the thing described in the reference, and the presence of such element therein would be so recognized by persons skilled in the art. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Further, inherency is not established by probabilities or possibilities, and the mere fact that a property may result from a given circumstances is not sufficient; instead it must be shown that such property *necessarily* inheres in the thing described in the reference. *Id.*

Main claim 43 requires that the fluorescent dye is *permeant* to the membrane of a biological cell; and that the masking dye is *substantially impermeant* to the membrane of the biological cell and *does not specifically bind* to the membrane of the biological cell. The Examiner says, in the sentence bridging pages 3-4 of the Office Action, that these are functional limitations of the combination and, since Alburger teaches the same combination, Alburger's combination would be able to perform the same functions.

Applicants respectfully disagree. Alburger does not, in fact, disclose any combination having these attributes and, therefore, does not disclose “the same combination” as is claimed. Alburger merely discloses a combination of a fluorescent dye and a masking dye. However, Alburger is completely silent about whether the fluorescent dye is permeant to the membranes of biological cells; or whether the masking dye is impermeant to the membranes of biological cells and also does not specifically bind to such membranes. Indeed, Alburger appears to be silent as to biological cells altogether.

The fact of the matter is that there are a wide variety of fluorescent and masking dyes known having various specifications, i.e., being membrane impermeant or not. The company **Invitrogen** is an example of a company offering such dyes.

Applicants attach copies of materials from Invitrogen’s website. Since these documents are being submitted as part of Applicant’s reply to the Office Action, consideration does not require formal compliance with the information disclosure statement rules. MPEP § 609.05(c).

The materials include four examples of cell-*impermeant* fluorescence dyes: EMA, nuclear yellow, propidium iodide, Fluorescent and Biotinylated Dextran. This information was found under the following link, where many more dyes can be found:

<http://www.invitrogen.com/site/us/en/home/References/Molecular-Probes-The-Handbook/tables/Properties-of-classic-nucleic-acid-stains.html>

and additional information (on Dextrans) can be found at:

<http://www.invitrogen.com/site/us/en/home/References/Molecular-Probes-The-Handbook/Fluorescent-Tracers-of-Cell-Morphology-and-Fluid-Flow/Fluorescent-and-Biotinylated-Dextrans.html>

Thus, the Examiner is clearly incorrect in stating that simply because Alburger discloses a combination including a fluorescent dye, the fluorescent dye must be permeant to membranes of biological cells. This is possible, but *not necessarily* the case. The foregoing materials establish that many, many cell-*impermeant* fluorescent dyes are known. Consequently, the Examiner has not established that Alburger's fluorescent dyes are *necessarily* cell-permeant. Again, the *Robertson* decision clearly holds that possibilities, even probabilities, *are insufficient*. Inherency is not shown unless it is *necessarily* the case that the prior art has the claimed attributes. Alburger's fluorescent dye does not necessarily have the claimed attribute of being permeant to the membrane of a biological cell. Consequently, Alburger does not inherently meet the terms of the rejected claims.

Regarding the instant masking dyes, as noted above, they must be impermeant to the cell membrane and at the same time not bond specifically to the cell membrane. Masking dyes that do not have these attributes are well-known, for example, for use as dyes for "Vital staining" of cells. Attached is an article from Wikipedia, which lists in the chapter "Common biological stains" examples of staining dyes which are cell-*permeable* such as Acridine orange, Methylene blue, Nile blue, Nile red.

Thus, the Examiner is, again, clearly incorrect in stating that simply because

Alburger discloses a combination including a masking dye, the masking dye must be impermeant to membranes of biological cells and not bond specifically to such membranes. This is possible, but not necessarily the case, as the Wikipedia article establishes that many cell permeable dyes are known. Again, the *Robertson* decision clearly holds that possibilities, even probabilities, *are insufficient*. Inherency is not shown unless it is *necessarily* the case that the prior art has the claimed attributes. Alburger's masking dye does not necessarily have the claimed attributes of being impermeant to the membrane of a biological cell and not binding specifically to such membranes. Consequently, Alburger does not inherently meet the terms of the rejected claims.

In view of the foregoing, Applicants respectfully submit that this rejection is in error and, therefore, respectfully request that the Examiner reconsider and withdraw it. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicants acknowledge with appreciation the Examiner's indication that the prior art rejections have been withdrawn. In view of this development, the nonelected claims have been canceled without prejudice to the filing of a divisional application.

Claim 21 was rejected under 35 USC § 103(a) as being obvious over Alburger. In response, Applicants respectfully submit that this rejection was dependent upon Alburger anticipating main claim 43, which, as discussed above, is not, in fact, the case. Indeed, the Examiner finds Alburger fails to teach the claimed reduction of at least 70%, but this would have been obvious. The other claimed parameters are dealt with by the language

“Alburger has been discussed above,” meaning in connection with the anticipation rejection. Since the anticipation rejection is in error, the obviousness rejection must similarly fail as there is nothing in Alburger alone that renders obvious even the main claim, let alone claim 21.

In short, the Examiner should reconsider and withdraw this rejection as well. An early notice that this rejection also has been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,  
NORRIS McLAUGHLIN & MARCUS, P.A.

By /Kurt G. Briscoe/  
Kurt G. Briscoe  
Attorney for Applicant(s)  
Reg. No. 33,141  
875 Third Avenue - 8<sup>th</sup> Floor  
New York, New York 10022  
Phone: (212) 808-0700  
Fax: (212) 808-0844